Original Article

Association Between Ferritin Levels and Severity of COVID-19 in RSUP Dr. M. Djamil Padang

Elsa Purnama Sari, Irvan Medison, Russilawati

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas - RSUP dr. M Djamil Padang, West Sumatera, Indonesia

Abstract

Background: Ferritin is one of the inflammatory markers used to predict the severity of COVID-19. Early assessment of severity is expected to be a priority in disease management. This study aims to determine the association between ferritin levels and the severity of confirmed COVID-19 patients at dr. M. Djamil Hospital Padang.

Methods: This study is a retrospective cohort study on confirmed COVID-19 patients from January to May 2021. Chi-square analysis was calculated to assess the association between ferritin levels and clinical grade, the severity of the chest X-ray, and the level of need for oxygen therapy. To assess the risk opportunities for ferritin levels on each dependent variable, an association analysis was performed by calculating the Odds Ratio.

Results: Characteristics of the patients were mainly female (54.25%), aged more than 50 years (59,00%), a clinical grade above category 4 (54,75%), required oxygen therapy (74,75%), the severity of chest X-ray was mild (75.50%), ferritin level <500 ng/ml (52.75%) and had no comorbidities (51.25%). This study found that ferritin levels correlated with a clinical grade, severity of chest X-ray, and level of need for oxygen therapy with HFNC and ventilator (*P*<0.001). Ferritin levels >1000 ng/mL have a risk opportunity for clinical grade category 7 OR=8.28 (95% CI=2.69-25.41), severe chest X-ray severity OR=5.52 (95% CI=2.55-11.97), and need for oxygen therapy with HFNC and ventilator, OR=4.76 (95% CI=2.70-8.39) vs. OR=7.69 (95% CI=3.97-14.92).

Conclusion: High ferritin levels significantly increase the risk of severe clinical severity, severe chest X-ray, and the level of need for oxygen therapy using HFNC and a ventilator in COVID-19 patients.

Keywords: COVID-19, ferritin levels, severity

Corresponding Author:
Elsa Purnama Sari |
Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, RSUP Dr. M Djamil, Sumatera Barat, Indonesia|
elsapurnamasari2007@gmail.com

Submitted: November 21st, 2021
Accepted: June 27th, 2022
Published: July 28th, 2022

J Respirol Indones. 2022
Vol. 42 No. 3: 237–43
https://doi.org/10.36497/jri.v42i3.244

INTRODUCTION

Coronavirus Disease 2019 (COVID -19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV2). Indonesia is a country with confirmed COVID-19 cases and the highest death rate in Southeast Asia and occupies the second position in Asia after India. Since Indonesia first reported cases of COVID-19 on March 2, 2020, Indonesia has received 1,012,350 confirmed cases of COVID-19 and 24,468 cases of death (2.8% confirmed cases fatality rate) until January 26, 2021.[1] The number of confirmed cases of COVID-19 that occurred in West Sumatra until August 15, 2021, was 81,886 out of 639,348 tested people. The positive rate is 12.81%. There were 11,447 patients (13.98%), who died 1,794 (2.19%) and 68,645 (83.83%) patients who were treated.[2]

Medical Research subjects in COVID-19, including epidemiology, clinical presentation, laboratory tests, diagnosis, and disease therapy, are still undergoing. Several inflammatory markers have been shown to correlate with the COVID-19 severity, such as lymphopenia, high D-dimer, T lymphocytes, IL-1 and IL-6, and high ferritin values.[3]

The mechanism of hyperferritinemia in COVID-19 patients is explained based on three theories. First, ferritin synthesis increased due to increased proinflammatory cytokines such as IL-1β, TNF-, and IL-6. Second, cellular damage due to the inflammatory process can lead to leakage of intracellular ferritin, thereby increasing serum ferritin. Third, acidotic conditions and increased Reactive Oxygen Species (ROS) in COVID patients with ARDS can liberate ferritin from the cell. Ferritin, as a

marker of the inflammatory response, is expected to be a predictor factor in assessing the severity of the disease at the beginning of treatment and determining priorities in patient management. Early and rapid assessment supports the provision of more optimal therapy.[4]

Cheng et al. found that the median value of ferritin levels in the heavy group was 4.7 times higher than the non-heavy group (*P*=0.049).[5] The COVID-19 severity patients can also be assessed based on the chest X-ray and the level of need for oxygen therapy. Eroglu et al.'s study in Turkey obtained a chest X-ray score <5, which had a lower median ferritin level (92.1) than the median ferritin level in the group with a score of 5 (286.0) with *P*<0.001. A study by Barciela et al. in Spain found an association of higher ferritin levels with the use of a high flow nasal cannula (HFNC) with *P*=0037.[6]

This study aims to determine the association between ferritin levels and the severity of confirmed COVID-19 patients at RSUP dr. M. Djamil Padang.

METHODS

This retrospective cohort study was conducted from January 1, 2021, to November 30, 2021, at RSUP Dr. M. Djamil Padang. The entire study population was confirmed COVID-19 patients who were treated at RSUP Dr. M. Djamil Padang from January 1 to May 31, 2021. The convenience technique with inclusion criteria confirmed COVID-19 patients from the results of RT PCR/TCM SARS-CoV-2 taken from a nasal/nasopharyngeal swab and aged >18 years. Exclusion criteria were COVID-19 patients with incomplete medical record data, including demographic data, description of clinical severity, ferritin levels, chest X-ray, oxygen therapy, and comorbidities.

Clinical severity is the patient's most severe condition in the first 24 hours based on The WHO ordinal scale modified by Beigel et al.[7] consists of Category 3: hospitalized, not requiring oxygen therapy; Category 4: hospitalized, does not require oxygen therapy, needs medical treatment; Category 5: hospitalized, requires oxygen therapy; Category 6: hospitalized, requiring HFNC or NIV; Category 7: hospitalized, requiring mechanical ventilation or ECMO.

The baseline characteristic data is presented as a frequency distribution table. The analysis was performed using the SPSS version 21 program. The chi-square was done in the bivariate analysis to see the significance of the independent and dependent variables and the chance for each variable to continue the analysis using the test binary logistic regression on the dependent variable, which has two categories. Meanwhile, analysis was performed by multinomial logistic regression for the dependent variable with more than two categories. The final result can be interpreted if *P*<0.05, significant if the value of OR>1 is a risk factor, OR<1 is a preventive risk factor/protective factor, and OR=1 is not a risk/reference.

RESULTS

The baseline characteristics are described in Table 1. This study's patients were aged 50 years, with 236 people (59.00%) and 217 women (54.25%). The most clinical severity of COVID-19 patients were patients who needed oxygen therapy, as many as 219 patients (54.75%), consisting of category 5 is 95 people (23.75%), category 6 is 89 (22.25%), and category 7 is 35 people (8.75%). The results of this study obtained the most characteristics were ferritin levels <500 ng/mL in as many as 211 people (52.75%), mild chest X-ray severity in 302 people (75.50%), and 299 people requiring oxygen therapy (74.75%). Most patients in this study had no comorbidities (51.25%).

The association between ferritin levels and the clinical severity of confirmed COVID-19 patients can be seen in Table 2 and displays a significant analysis result (*P*<0.001). Ferritin levels >1000 ng/mL provide an opportunity for the severity of category 3 (OR=3.45, 95% CI=1.89–6.27), category 4 (OR=14.17, 95% CI=3.36–59.67), category 5 (OR=2.82, 95% CI=1.62–4.92), category 6 (OR=6.97, 95% CI=3.75–12.99), and category 7 (OR=8.28; 95% CI=2.69–25.41).

Table 1. The Baseline characteristics of Confirmed COVID-19 Patients Treated at RSUP Dr. M. Djamil Padang

Patient Characteristics	Total (n= 227)	%
Aged		
<50 years	164	41,00
≥50 years	236	59,00
Gender		
Female	217	54.25
Male	183	45,75
Clinical Severity		
Category 3	119	29,75
Category 4	62	15,50
Category 5	95	23,75
Category 6	89	22,25
Category 7	35	8,75
Ferritin Levels		
<500 ng/mL	211	52,75
500–1000 ng/mL	73	18,25
>1000 ng/mL	116	29,00
Chest X-ray Severity		
Mild	302	75,50
Moderate	59	14,75
Severe	39	9,75
Need for Oxygen Therapy		
Free air	101	25,25
Oxygen Therapy	299	74,75
Nasal Cannulae	52	13,00
NRM	70	17,50
HFNC	95	23,75
Ventilator	82	20,50
Number of Comorbidities		
No Comorbid	205	51,25
1 Comorbid	110	27,50
>1 Comorbid	85	21,25
Comorbid Type		
Hypertension	107	26,75
Diabetes Mellitus	69	17,25
Cardiovascular Disease	39	9,75
Chronic Kidney Disease	30	7,50
Obesity	28	7,00
Malignancy	17	4,25
Chronic Lung Disease	9	2,25
Cerebrovascular Disease	8	2,00
Chronic Liver Disease	6	1,50
Immunodeficiency	2	0,50

The association between ferritin levels and risk opportunities in the chest X-ray severity can be seen in Table 3, and the analysis results obtained a significant association (*P*<0.001). Most patients were patients who had ferritin levels <500 ng/mL, as many as 211 people (52.75%), and most (61.26%) had a mild severity of chest X-rays. While patients with ferritin levels >1000 ng/mL, 116 patients (29%) had the highest severity of chest X-ray, which was the heavy group (25 patients (64%)).

The results of the statistical test showed the probability of the risk of ferritin levels on the severity of the chest X-ray at a ferritin level of 500-1000 ng/mL associated with moderate severity (OR=2.64, 95% CI=1.20–5.80) and mild (OR=2.16, 95% CI=1.09–4.27). Meanwhile, ferritin levels >1000 ng/mL were associated with severe severity (OR=5.52, 95% CI=2.55–11.97), moderate (OR=4.25, 95% CI=2.20–8.21) and mild (OR=2.42, 95% CI=3.71–11.11).

In Table 4, the statistical tests showed a significant association between ferritin levels and the need for oxygen therapy, HFNC, and ventilators (*P*<0.001). However, there was no correlation between ferritin levels and the need for nasal cannula oxygen therapy and NRM (*P*=0.120 and *P*=0.172, respectively). Ferritin levels >1000 ng/mL have the opportunity to need oxygen therapy with a ventilator (OR=7.69, 95% CI=3.97–14.92) and HFNC (OR=4.76, 95% CI=2.70–8.39).

Table 2. Association between ferritin levels and risk opportunities on the clinical degree of COVID-19 patients

Clinical Severity		Ferritin Levels			Total	*P*
		<500 ng/mL	500–1000 ng/mL	>1000 ng/mL		
Cat 3	**(N/%)**	86 (72.27%)	19 (15.97%)	14 (11.76%)	119 (100%)	<0.001
	OR (95% CI)	Ref	1.69 (0.92–3.08)	3.45 (1.89–6.27) *	---	
Cat 4	**(N/%)**	51 (82.25%)	9 (14.52%)	2 (3.23%)	62 (100%)	<0.001
	OR (95% CI)	Ref	2.34 (1.00–5.48) *	14.17 (3.36–59.67) *	---	
Cat 5	**(N/%)**	43 (45.26%)	21 (22.11%)	31 (32.63%)	95 (100%)	<0.001
	OR (95% CI)	Ref	2.21(1.15-4.24) *	2.82 (1.62–4.92)	---	
Cat 6	**(N/%)**	25 (28.09%)	18 (20.22%)	46 (51.69%)	89 (100%)	<0.001
	OR (95% CI)	Ref	3.46 (1.66–7.23) *	6,97 (3.75–12.99)	---	
Cat 7	**(N/%)**	6 (17.14%)	6 (17.14%)	23 (65.72%)	35 (100%)	<0.001
	OR (95% CI)	Ref	3.00 (0.73–12.32)	8,28 (2.69–25.41) *	---	

Table 3. Association between ferritin levels and risk opportunities on the severity of chest X-rays of COVID-19 patients

The Chest X-ray Severity		Ferritin Levels			Total	*P*
		<500 ng/mL	500–1000 ng/mL	>1000 ng/mL		
Mild	(N/%)	185 (61.26%)	56 (18.54%)	61 (20.20%)	302 (100%)	<0.001
	OR (95% CI)	Ref	2.16 (1.09–4,27) *	2.42 (3.71–11.11) *	---	
Moderate	(N/%)	16 (27.12%)	13 (22.03%)	30 (50.85%)	59 (100%)	<0.001
	OR (95% CI)	Ref	2.64 (1.20–5.80) *	4.25 (2.20–8.21) *	---	
Severe	(N/%)	10 (25.64%)	4 (10.26%)	25 (64.10%)	39 (100%)	<0.001
	OR (95% CI)	Ref	1.17 (0.35–3.84)	5.52 (2.55–11.97) *	---	

Note=*P<0.05 significance; *Pearson chi-square test*; *multinomial logistic regression*; Ref:Reference

Table 4. Association between ferritin levels and risk opportunities on the oxygen therapy needs of COVID-19 patients

Need for Oxygen Therapy		Ferritin Levels			Total	*P*
		<500 ng/mL	500–1000 ng/mL	>1000 ng/mL		
Free air	(N/%)	87 (86.14%)	13 (12.88%)	1 (0.99%)	101 (100%)	<0.001
	OR (95% CI)	Ref	1.17 (1.17–2.39) *	1.74 (1.66–1.87) *	---	
Nasal cannula	(N/%)	40 (76.92%)	10 (19.23%)	2 (3.85%)	52 (100)	0.120
	OR (95% CI)	Ref	1.05 (0.46–2.36)	0.41 (0.16–1.02)	---	
NRM	(N/%)	40 (57.14%)	13 (18.57%)	17 (24.29%)	70 (100%)	0.172
	OR (95% CI)	Ref	1.69 (0.81–3.52)	1.72 (0.91–3.25)	---	
HFNC	(N/%)	28 (29.47%)	19 (20%)	48 (50.53%)	95 (100%)	<0.001
	OR (95% CI)	Ref	2.02 (0.99–4.09)	4.76 (2.70–8.39) *	---	
Ventilator	(N/%)	16 (19.51%)	18 (21.95%)	48 (58.54%)	82 (100%)	<0.001
	OR (95% CI)	Ref	3.64 (1.66–7.98*)	7.69 (3.97–14.92) *	---	

Note=*P<0.05 significance; *chi –square test*; *binary logistic regression*; Ref:reference

DISCUSSION

The baseline characteristics showed that most COVID-19 patients were treated at RSUP dr. M. Djamil Padang is mainly 50 years (59.00%). Perrotta et al. found that age is related to the severity of COVID-19 disease. Age causes significant changes in the immune response and chronic inflammatory processes.[6] One of the main signs of aging in the immune system is a reduction in the number of lymphocytes associated with the involution of the thymus, a reduction in hematopoietic cells, and inadequate peripheral regulation.[8]

Most gender displayed in this study is female (54.3%) and male (45.8%). This study's results align with the results of Sensusiati et al. in Surabaya (51.4%) and Ni et al. in China (52%).[8,9] Chen et al. showed that ACE2 expression increased up to 100% in Asian women in the adrenal glands, adipose tissue, esophagus, and heart. ACE2 expression also increases in the lungs, blood vessels, colon, and adrenal glands.[10]

The most severe COVID-19 patients in this study are categories above category 4 with a total of 219 (54.75%), consisting of category 5 (23.75%), category 6 (22.25%), and category 7 (8.75%). Beigel et al. found that the highest number was above category 4, with category 5 being the most (41%).[7] The highest need for oxygen therapy was 299 (74.75%) patients requiring oxygen therapy, consisting HFNC (23.75%), ventilator (20.50%), NRM (17.50%), and nasal cannula (13,5%). While patients who do not need oxygen therapy (free air) as much as 25.25%. The most commonly used oxygen therapy is HFNC. The number of COVID-19 patients increased rapidly in a short time during the COVID-19 outbreak, and many experienced a sudden worsening. This condition increases the need for intensive care facilities, and HFNC becomes essential. HFNC is considered easier to operate, not limited to pulmonology or intensive care specialists.[11]

Most of the patients' radiological features were mild (75.50%). Sathi's study in India also used the RALE score in his study and obtained the same results, namely the distribution of severity of chest X-rays in the mild group (45%).[11] The highest ferritin level in this study was <500 ng/mL (52.75%). This study's results align with the research of Ghwell et al.,

who found the highest ferritin levels <350 ng/mL (51.51%).[12]

This study found that more than 50% of patients did not have comorbid diseases (51.25%), comparable to Surendra et al. in Jakarta, which found that most patients did not have comorbidities (69%).[1] Patient with one or more comorbidities is associated with a poor outcome. Khedr et al concluded that the number of comorbidities was a risk factor for death. Patients with 3 or more comorbidities had an HR of 2.9 (95% CI=1.5-5.6).[13] The three most comorbid patients in this study were hypertension (26.75%), diabetes mellitus (17.25%), and cardiovascular disease (9.75%).

In this study, there was a significant association between ferritin levels and the clinical severity of patients (*P*<0.001), as presented in Table 5.2. Ferritin levels more than 1000 ng/mL risk 8.28 times higher for the occurrence of severity category 7 (95% CI=2.69-25.41). High ferritin levels significantly increase the risk of a more severe clinical severity in the patient. Ghweil et al. found an association between ferritin and patient severity (95% CI=1.01-1.03) with *P*<0.001.[12.] Dahan et al. found that the mean ferritin level in the severe patient group (2817.6 ng/mL) was higher than the non-severe group (708.6 ng/mL).[14]

Ferritin acts as an iron binder and plays a role in inflammatory processes and the immune system.[5] The mechanism of hyperferritinemia in COVID-19 patients can be explained based on three emerging theories. First, increased ferritin synthesis caused increased proinflammatory cytokines such as IL-1β, TNF-, and IL-6. Second, cellular damage due to the inflammatory process can lead to leakage of intracellular ferritin, thereby increasing serum ferritin. Third, acidotic conditions and increased ROS in COVID patients with ARDS can liberate ferritin from the cell.[15]

Research on clinical features and laboratory biomarkers shows COVID-19 as part of the hyperferritinemia syndrome.[16] Hyperferritinemia syndrome is a collection of several diseases that exhibit hyper inflammation and hyperferritinemia, some of which are life-threatening. Hyperferritinemia is a body condition characterized by more than 500 g/ml serum levels. Four clinical groups of diseases have been classified as hyperferritinemia syndrome: macrophage activation syndrome (MAS), adult-onset Still's a disease (AOSD), catastrophic APS (CAPS), and septic shock.[17] In addition to the process of infection and inflammation, the levels of ferritin in the body are influenced by gender, age, hypoxic conditions, the amount of iron intake, chronic liver disease, kidney disease, and malignancy.[18] These conditions can act as a confounding factor in this study.

This study found a correlation between ferritin levels and chest X-ray severity (*P*<0.001). Ferritin levels >1000 ng/mL, 5.52 times higher risk for the occurrence of severe chest X-ray findings. High ferritin levels significantly increase the risk of severe chest radiographic severity in COVID-19 patients. The study's finding comparable with Eroglu et al. in Turkey, which found that the group with a chest X-ray score <5 had a lower median ferritin level (92.1) than the median ferritin level in the group with a score of 5 (286.0) with *P*<0.001.[18]

Kaleemi et al received a chest x-ray severity score (CXR-SS) of 5-8 at the time of the patient's initial admission to the hospital, which was associated with a predictable ICU stay (*P*<0.001) and mortality (*P*<0.001).[19] This study is in line with that of Borghesi et al., who found that patients with high Brixia scores on chest X-rays were associated with a higher risk of death in the hospital (*P*<0.0001).[20] In addition, Sensusiati et al. in Surabaya found a RALE score >2 increased patient mortality up to 7 times. [9] Rapid chest X-ray examination can be an initial reference when providing therapy to patients. The limitations of CT scans and radiologists, especially in Indonesia, make chest X-rays an essential examination in establishing a diagnosis and determining the severity of COVID-19 patients.[21]

This study found a correlation between ferritin levels and chest X-ray severity (*P*<0.001). Ferritin levels >1000 ng/mL, 5.52 times higher risk for the occurrence of severe chest X-ray findings. High ferritin levels significantly increase the risk of severe chest radiographic severity in COVID-19 patients.

This study has resulted in line with the study of Eroglu et al. in Turkey, which found that the group with a chest X-ray score <5 had a lower median ferritin level (92.1) than the median ferritin level in the group with a score of 5 (286.0) with *P*<0.001.[18]

LIMITATION

This research has the limitation is that the sampling technique is carried out without selection of factors confounders that affect the ferritin content and composition of the sample size as well not equal so that it could lead to bias in this study.

CONCLUSION

Characteristics of COVID-19 patients treated at RSUP dr. M. Djamil Padang were primarily women aged more than 50 years, with a clinical grade above category 4, requiring oxygen therapy, mild radiological features, and almost half ferritin levels of 500 ng/mL, and had no comorbidities. High ferritin levels significantly increase the risk of severe clinical severity, severe chest X-ray, and the level of need for oxygen therapy using HFNC and a ventilator in COVID-19 patients.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCES

1. Surendra H, Elyazar IR, Djaafara BA, Ekawati LL, Saraswati K, Adrian V, et al. Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: A hospital-based retrospective cohort study. Lancet Reg Heal - West Pacific. 2021;9:100108.
2. Tang D, Comish P, Kang R. The hallmarks of COVID-19 disease. PLoS Pathog. 2020;16(5):e1008536.
3. Bozkurt FT, Tercan M, Patmano G, Bingol Tanrıverdi T, Demir HA, Yurekli UF. Can ferritin levels predict the severity of illness in patients with COVID-19? Cureus. 2021;13(1):e12832.
4. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal. 2020;34(10):e23618.
5. Riveiro-Barciela M, Labrador-Horrillo M, Camps-Relats L, González-Sans D, Ventura-Cots M, Terrones-Peinador M, et al. Simple predictive models identify patients with COVID-19 pneumonia and poor prognosis. PLoS One. 2020;15(12):e0244627.
6. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clin Exp Res. 2020;32(8):1599–608.
7. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020;383(19):1813–26.
8. Ni Y-N, Wang T, Liang B-M, Liang Z-A. The independent factors associated with oxygen therapy in COVID-19 patients under 65 years old. PLoS One. 2021;16(1):e0245690.
9. Sensusiati AD, Amin M, Nasronudin N, Rosyid AN, Ramadhan NA, Lathifah R, et al. Age, neutrophil lymphocyte ratio, and radiographic assessment of the quantity of lung edema (RALE) score to predict in-hospital mortality in COVID-19 patients: a retrospective study. F1000Research. 2020;9:1286.
10. Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Aging Cell. 2020;19(7):e13168.
11. Sathi S, Tiwari R, Verma S, Kumar Garg A, Singh Saini V, Kumar Singh M, et al. Role of chest x-ray in coronavirus disease and correlation of radiological features with clinical outcomes in indian patients. Can J Infect Dis Med Microbiol. 2021;2021:6326947.

12. Ghweil AA, Hassan MH, Khodeary A, Mohamed AO, Mohammed HM, Abdelazez AA, et al. Characteristics, Outcomes and Indicators of Severity for COVID-19 Among Sample of ESNA Quarantine Hospital's Patients, Egypt: A Retrospective Study. Infect Drug Resist. 2020;13:2375–83.
13. Khedr EM, Daef E, Mohamed-Hussein A, Mostafa EF, Zein M, Hassany SM, et al. Impact of comorbidities on COVID-19 outcome. medRxiv : the preprint server for health sciences. 2020.
14. Dahan S, Segal G, Katz I, Hellou T, Tietel M, Bryk G, et al. Ferritin as a Marker of Severity in COVID-19 Patients: A Fatal Correlation. Isr Med Assoc J. 2020;22(8):494–500.
15. Kappert K, Jahić A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers. 2020;25(8):616–25.
16. Perricone C, Bartoloni E, Bursi R, Cafaro G, Guidelli GM, Shoenfeld Y, et al. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. Immunol Res. 2020;68(4):213–24.
17. M Hussein A, Taha ZB, Gailan Malek A, Akram Rasul K, Hazim Kasim D, Jalal Ahmed R, et al. D-Dimer and Serum ferritin as an independent risk factor for severity in COVID-19 patients. Mater today Proc. 2021;
18. Aydoğan Eroğlu S, Çagavi Z, Yıldız T, Karakurt Z, Group OBOCI. Can the usage of the chest x-ray scoring during hospitalization in patients with COVID-19 predict the severity of the disease? Turkish Thorac J. 2021;22(3):190–8.
19. Kaleemi R, Hilal K, Arshad A, Martins RS, Nankani A, Tu H, et al. The association of chest radiographic findings and severity scoring with clinical outcomes in patients with COVID-19 presenting to the emergency department of a tertiary care hospital in Pakistan. PLoS One. 2021;16(1):e0244886.
20. Borghesi A, Zigliani A, Golemi S, Carapella N, Maculotti P, Farina D, et al. Chest X-ray severity index as a predictor of in-hospital mortality in coronavirus disease 2019: A study of 302 patients from Italy. Int J Infect Dis. 2020;96:291–3.
21. Setiawati R, Widyoningroem A, Handarini T, Hayati F, Basja AT, Putri ARDS, et al. Modified Chest X-Ray Scoring System in Evaluating Severity of COVID-19 Patient in Dr. Soetomo General Hospital Surabaya, Indonesia. Int J Gen Med. 2021;14:2407–12.